

## REMARKS

Claim 22 has been canceled without prejudice or disclaimer. Claims 1-10, 15 and 19 have been amended. Claims 18, 20 and 21 and claims 11-14 were previously withdrawn or cancelled, respectively. Claims 23-25 have been added. Subsequent to the entry of the present amendment, claims 1-10, 15-17, 19 and 23-25 are pending and at issue. These amendments and additions add no new matter as the claim language is fully supported by the specification and original claims.

### **I. Amendments and Objections to the Claims**

Claims 1, 15 and 19 are objected to for use of improper sequence identifiers, and claims 1 and 19 for containing non-elected subject matter. Claims 1, 15 and 19 have been amended to delete the amino acid sequence relating to the sequence identifiers. Claims 1 and 19 have also been amended to limit the claims to the elected subject matter, or SEQ ID NO:8.

Multiple dependent claims 16 and 17 are objected to because they depend on claim 15, another multiple dependent claim. Claim 15 has been amended such that it is no longer a multiple dependent claim. Hence Applicants respectfully request the withdrawal of the objections to claims 16 and 17 which is made moot by the amendment of claim 15.

Claim 22 has been canceled without prejudice or disclaimer. Further, those claims depending on claim 22, e.g., claims 1-4, 10, 15 and 19, have been amended accordingly.

Claims 23-25 have been added. Support for claims 23-25 can be found in the specification as filed, e.g., Examples 17-26.

Further, claims 4-9 have been amended to replace the term "suspension" with the term "solution." This amendment has support in the specification as filed on page 12, line 34 and page 13, line 28.

Thus, the above amendments are fully supported by the specification and claims as filed, and no new matter has been added.

**II. Rejections under 35 U.S.C. §112, First Paragraph (written description)**

Claims 2-10, 15, 19 and 22 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to describe in the specification in such a way as to reasonably convey to one skilled in the art that the Applicant, at the time of filing, had possession of the claimed invention. Applicant traverses this rejection as it may apply to the amended claims.

The rejection is moot as it relates to claim 22 and claims, directly or indirectly, dependent on claim 22, for example, claim 2-10, 15 and 19.

Accordingly, withdrawal of rejection of claims 2-10, 15, 19 and 22 under 35 U.S.C. § 112, first paragraph is respectfully requested.

**III. Rejections under 35 U.S.C. § 103(a)**

Claims 1-10, 15, 19 and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Tamburini et al. (WO97/33996) in view of Rasche et al. and O’Riordan et al. (hereinafter, “Tamburini”, “Rasche,” and “O’Riordan,” respectively). Applicants respectfully traverse this rejection as it may apply to the amended claims.

According to the Office Action, the prior art allegedly provides a method of increasing the rate of mucociliary clearance as the claimed invention (see page 8 of the Office Action).

To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

*(1) No suggestion or motivation to combine*

The Office Action suggests that a combination of the above references would result in the claimed invention. However, there is no suggestion in any of the references for the proposed combination. As the CAFC stated in *ACS Hospital Systems Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (1984):

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined *only* if there is some suggestion or incentive to do so.

Furthermore, in *In re Gordon*, 221 USPQ 1125, 1127 (Fed.Cir. 1984), *citing In re Sernaker*, 217 USPQ 1, 6-7 (Fed. Cir. 1983) and *In re Imperato*, 179 USPQ 730, 732 (CCPA 1973):

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.

Although one cannot show obviousness by attacking each reference individually where the rejection is based on the combination, the prior art *still* has to suggest or provide incentive for the combination. This suggestion or incentive is not found in the Tamburini, Rasche or O’Riordan, because: Tamburini which discloses bikunin as inhibitors of various serine proteases does not suggest any method of accelerating the rate of mucociliary clearance; Rasche which tests the therapeutic affects of aprotinin does not suggest that a Kunitz-type inhibitor to accelerate the rate of mucociliary clearance (described in more detail below); and O’Riordan which discloses that agents having anti-elastase activity may be beneficial in blocking mucociliary impairment does not suggest that a Kunitz-type inhibitor can be used to treat mucociliary impairment because elastase activity has not been indicated in mucociliary impairment or dysfunction. That is, the function of a Kunitz-type inhibitor was not known in the art at the time of filing, and is not suggested in any of the cited references. Thus, “[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.” See *ACS Hospital Systems, supra*.

Therefore, absent *any* suggestion or motivation to combine the references, there is no obviousness rejection.

*(2) No reasonable expectation of success*

Obviousness requires a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); MPEP § 2143.02. Further, predictability is determined at the time the invention was made. Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Interf. 1986); MPEP § 2143.02.

Reasonable expectation of success has not been established because the combination of the cited references suggests that a Kunitz-type serine protease inhibitor affects proteases which somehow result in improved mucociliary function. However, affecting elastase activity or levels does not correlate or is not relevant to accelerating the rate of mucociliary clearance as claimed. For example, at the time of filing of the instant application, Laube et al. (1996) showed that upon treatment with DNase, a protease inhibitor, forced expiratory volume (FEV) is improved but mucociliary clearance is not. See Exhibit A, Laube et al. (1996), "Effect of rhDNase on airflow obstruction and mucociliary clearance in Cystic Fibrosis," *Respir Crit Care Med*, 153: 752-756. Thus, at the time of filing, there would have been no reasonable expectation of success by combining Tamburini, Rasche and O'Riordan. Although modifying the art to arrive at the claimed invention is permissible, modification of the art cannot exist absent some suggestion or teaching of the desirability of the modification; and in its absence no reasonable expectation of success of the claimed invention can be asserted.

*(3) Not all claim limitations are taught*

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA

1974); MPEP § 2143.03. Further, if an independent claim is nonobvious under 35 U.S.C. § 103, then any claim depending there from is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP § 2143.03.

It is also well established that determining obviousness under 35 U.S.C. § 103 requires an analysis of the claimed invention *as a whole*, and focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify that determination. *Gillette Co. v. S.C. Johnson & Son Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990). Thus, changes from the prior art, must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make such changes to produce the claimed invention. *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1324 (Fed. Cir. 1990); also see *Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 (Fed. Cir. 2004).

Applicants submit that the combination of references imply that the treatment lies in balancing the levels of anti-proteases and proteases: i) Rasche states that “[i]t cannot be deduced from [their] studies that protease inhibitors administered *in vivo* is really able to bind proteases from decayed leucocytes and bacterial in the bronchial space...the inhibitor problem seems to be a central factor.” See page 8, last paragraph before the Summary (Rasche et al. translated document); ii) O’Riordan states that their “data indicate that the antigen-induced impairment of mucociliary clearance is partly dependent on increased elastase activity, and that elastase inhibitors may be useful in protecting against mucociliary dysfunction.” See last sentence of the O’Riordan Abstract; and iii) Tamburini teaches that bikunin inhibits various serine proteases. Thus, the cited references, alone or in combined, indicate that inhibitors of proteases (e.g., elastases) can be used to treat of mucociliary clearance; however, that is not the claimed invention.

Applicants submit, that *as a whole*, the claimed invention does not imply or indicate that accelerating the rate of mucociliary clearance by the Kunitz-type inhibitors results from balancing the levels of inhibitors versus proteases. Rather, the invention *as a whole* describes

that Kunitz-type inhibitors accelerate the rate of mucociliary clearance by inhibiting sodium channels and affecting the potential difference, thereby increasing the TMV (see Examples 17-26); and *not* inhibiting proteases by increasing levels of protease inhibitors.

The “as a whole” analysis, takes into consideration that inventions typically are new combinations of existing principles or features. *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698 [218 USPQ 865] (Fed. Cir. 1983) (noting that “virtually all [inventions] are combinations of old elements”). The “as a whole” instruction in title 35 prevents evaluation of the invention part by part. That is, the determination of whether a novel structure is or is not ‘obvious’ requires cognizance of the properties of that structure and the problem which it solves, viewed in light of the teachings of the prior art. See *Ruiz, supra*.

Where the invention for which a patent is sought solves a problem which persisted in the art, we must look to the problem as well as to its solution if we are to properly appraise what was done and to evaluate it against what would be obvious to one having the ordinary skills of the art.

The problem solved by the claimed invention, contrary to the what was understood in the art at the time of filing, is that Kunitz-type inhibitors function to accelerate mucociliary clearance not because they inhibit proteases released from antigen induced inflammatory reaction mechanisms (as in Tamburini, Rasche and O’Riordan) but because they inhibit sodium channels and reduce potential difference, thereby increasing TMV.

Thus, for all the foregoing reasons, Tamburini in view of Rasche and O’Riordan cannot make the claimed invention obvious, because at the time of filing of the claimed invention, the combined references: i) did not suggest or motivate one skilled in the art to combine the references; ii) there was no reasonable expectation of success even if the references were combined; and iii) not all the claim limitations were obvious from the combined references. Therefore, there is no *prima facie* case of obviousness and the claimed invention is patentable over the art.

Also, Bridges et al. (2001) is a post-filing journal article, co-authored by Hall, R. L., who is also a co-inventor in the claimed invention that describes and further supports the disclosure of the claimed invention. See Exhibit B, Bridges et al. (2001) "Na<sup>+</sup> transport in normal and CF human bronchial epithelial cells is inhibited by BAY 39-9437," *Am J Physiol Lung Cell Mol Physiol* 281:L16-L23. Bridges et al. describe that BAY 39-9437, a Kunitz-type protein of the claimed invention, inhibits sodium current or transport, thereby improving mucociliary clearance (see page L22, col. 1, last paragraph). The claimed invention and Bridges et al. show, that although Kunitz-type proteins inhibit various serine proteases, as of the filing date of the claimed invention, the various proteases known to be inhibited by Kunitz-type proteins (e.g., trypsin, human tissue and plasma kallikrein and neutrophil elastases) were not directly linked or relevant to mucociliary clearance. In fact, prostatic, a protease which has been shown to be directly involved in reducing Na<sup>+</sup> transport by activating the epithelial sodium channel (ENaC), was not known until after the time of the filing of the claimed invention; which although not disclosing prostatic *per se*, describes similar experiments and results (Examples 17-26) as that in Bridges et al., which does suggest the role of prostatic in regulating the ENaC.

Further, regulation of ENaC in human airways by prostatic is directly implicated in Donaldson et al. (2002). See Exhibit C, Donaldson, S. H. et al., "Regulation of the epithelial sodium channel by serine proteases in human airways," *J Biological Chemistry* 277(10):8338-8345. Thus, the claimed invention was the first to disclose and suggest a direct role of a protease not yet reported and which inhibition may affect the Na<sup>+</sup> transport as a method to accelerate of mucociliary clearance.

Accordingly, withdrawal of rejection of claims 1-10, 15, 19 and 20 under 35 U.S.C. § 103(a) is respectfully requested.

In re Application of:  
Hall et al.  
Application No.: 09/441,966  
Filed: November 17, 1999  
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Patent  
Atty. Docket No.: AERO1120-1

### Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicant's undersigned representative if there are any questions relating to this application.

Applicants do not believe any other fees are due in connection with this submission, however if any other fees are due, please charge any fees, or make any credits, to Deposit Account No. 07-1896.

Respectfully submitted,

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